REMARKS

Reconsideration is requested.

Claims 1-65 have been canceled, without prejudice.

Claims 66-104 have been added and are pending. The claims have been amended to advance prosecution and without prejudice.

Support for the amended claims may be found throughout the specification, including the originally-filed claims. No new matter has been added. At a minimum, the pending claims are patentable over the art of record, as further detailed below.

Specifically, the following description of the correspondence between the canceled and amended claims is provided for the Examiner's convenience.

Claims 66 and 67 correspond to now-canceled claim 7. Claim 68 corresponds to now-canceled claim 8. Claim 69 corresponds to now-canceled claim 9. Claim 70 corresponds to now-canceled claim 10. Claim 71 corresponds to now-canceled claim 11. Claim 72 corresponds to now-canceled claim 12. Claim 73 corresponds to now-canceled claim 13. Claim 74 corresponds to now-canceled claim 14. Claim 75 corresponds to now-canceled claim 19. Claim 76 corresponds to now-canceled claim 21 with the additional indication of homozygous disruption. Claim 77 corresponds to now-canceled claim 22 with the additional indication of homozygous disruption. Claim 78 corresponds to now-canceled claim 23 with the additional indication of homozygous disruption. Claim 79 corresponds to now-canceled claim 24 with the additional indication of homozygous disruption. Claim 80 corresponds to now-canceled claim 31. Claim 81 corresponds to now-canceled claim 32, which contains a recitation similar to claim 19, now claim 75. Claim 82 corresponds to now-canc led claim 32 with the

additional recitation of the presence of a CTG repeat. Claim 82 corresponds to now-canceled claim 32 with the additional recitation of the presence of a CTG repeat that encodes leucine. Claim 84 corresponds to now-canceled claim 33. Claim 85 corresponds to now-canceled claim 35. Claim 86 corresponds to now-canceled claim 36. Claim 87 corresponds to now-canceled claim 37. Claim 88 corresponds to now-canceled claim 39. Claim 89 corresponds to now-canceled claim 39. Claim 90 corresponds to now-canceled claim 40. Claim 91 corresponds to now-canceled claim 41. Claim 92 corresponds to now-canceled claim 42. Claim 93 corresponds to now-canceled claim 43. Claim 94 corresponds to now-canceled claim 44. Claim 95 corresponds to now-canceled claim 47. Claim 96 corresponds to now-canceled claim 48. Claim 97 corresponds to now-canceled claim 49. Claim 98 corresponds to now-canceled claim 50. Claim 99 corresponds to now-canceled claim 51. Claim 100 corresponds to now-canceled claim 52. Claim 101 corresponds to now-canceled claim 57. Claim 102 corresponds to now-canceled claim 58. Claim 103 corresponds to now-canceled claim 59. Claim 104 corresponds to now-canceled claim 60.

No new matter has been added. As claims 7-14, 19, 21, 31, 35-44 and 47-52, were indicated to be patentable over the art of record, the applicant submits, at a minimum, that claims 66-76, 80 and 85-100 are similarly patentable over the art of record and an indication of the same in the Examiner's next communication is requested.

The specification has been amended to delete the hyperlink notation objected-to by the Examiner at page 3 of the Office Action dated July 5, 2002 (Paper No. 13). Withdrawal of the objection to the specification is requested.

Reconsideration of the restriction requirement and rejoinder and examination of at least claims 57-60 (now claims 101-104) are requested, for at least the following reasons.

The Examiner has asserted that the subject matter of claims 58-60 (now claims 102-104, respectively) (Group V) has "required a separate status in the art as a separate subject for inventive effort and require independent searches." See, page 2 of Paper No. 13. The Examiner has admitted however on page 2 of the Office Action dated February 22, 2002 (Paper No. 10) that the subject matter of the elected Group I and the subject matter of claims 58-60 (Group V) are both classified in class 435, subclasses 325 and 320.1. Accordingly, the subject matter of the Examiner's Groups I and V have not acquired a separate status in the art as separate subject matter for inventive effort which requires independent searches and the subject matter of the Examiner's Groups I and V should be examined together. The search of the subject matter of the Examiner's Groups I and V would not be an undue burden on the Examiner, as indicated by the applicant's Response of April 22, 2002. Contrary to the Examiner's assertions, a search of the subject matter of the Examiner's Groups I and V would be coextensive with regard to a literature search, as evidenced by the Examiner's own classification. Examination of the subject matter of the Examiner's Group V with the elected Group I is requested.

Moreover, the subject matter of the Examiner's Group IV should be examined with the subject matter of the elected Group I. The subject matter of claim 57 (now claims 101) (which separately defines the withdrawn Group IV) is similar to the subject matter of the examined, and elected, Group I, as defined by claim 47 (now claim 95).

Specifically, each of claims 47 (now claim 95) and 57 (now claim 101) provide a method of identifying agents capable of affecting a phenotype of a knock-out mouse or cell line. The method of claim 47 (now claim 95) involves administering a putative agent to the knock-out mouse of claim 32 (now claim 81) whereas the method of claim 57 (now claim 101) involves contacting the knock-out cell of claim 53 (now incorporated in claim 101) with a putative agent. The mouse of claim 32 (now claim 81) and the cell of claim 53 (now recited in claim 101) and the method of claim 47 (now claim 95) have each been included in the Examiner's definition of Group I whereas the method of claim 57 (now claim 101) has been alleged to define a separately patentable Group. The applicant submits, with due respect, that this separate classification of the subject matter of claim 57 is inconsistent and rejoinder and examination of the subject matter of claim 57 (claim 101) with the subject matter of the elected Group I are requested. Search of the subject matter of claim 57 (now claim 101) would not be an undue burden on the Examiner as noted by the applicant in the Response of April 22, 2002.

Examination of claims 101-104 is requested.

The Section 101 rejection of claims 1-47 and 53-56 is moot in view of the arguments provided below. The claims are submitted to define patentable subject matter and consideration of the following in this regard is requested.

The Examiner has recognized that the specification asserts a utility for the presently claimed invention which includes methods of identifying agents capable of affecting a phenotype of a knock-out mouse; methods for treatment of bone disease, cartilage disease or kidney disease by administering to an appropriate subject an agent capable of affecting the phenotype of a knock-out mouse; methods of determining

whether expansion of a trinucleotide repeat in a TRP produces a phenotypic change utilizing knock-out st m cells; and production of TRP gene products. See, pages 5-6 of Paper No. 13.

The Examiner has quoted extensively from the "REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS" at pages 3-5 of Paper No. 13 as allegedly supporting the Section 101 rejection. The Examiner has indicated the cited Guidelines are available at http://www.uspto.gov/web/menu/utility.pdf. The following Example 11 is provided in the Guidelines as a Patent Office example of how the Guidelines, and hence the Patent Office interpretation of Section 101, are to be applied in the area of claims directed to transgenic animals.

> **Example 11: Animals with Uncharacterized Human Genes**
> **Specification:** Kidney cells from a patient with Polycystic Kidney **(PCK) Disease** have been used to make a cDNA library. From this library 8000 nucleotide **"fragments" have been sequenced** but not yet used to express proteins in a transformed host cell **nor have they been characterized in any other way**. The 50 longest fragments, SEQ ID NO: 1-50, respectively, have been used to make transgenic mice. **None of the 50 lines of mice have developed Polycystic Kidney Disease to date**. The asserted utility is the use of the mice to research human genes from diseased human kidneys. The disease is inheritable, but **chromosomal loci have not yet been identified. Neither the absence or presence of a specific protein has been identified with the disease condition.**
>
> **Claims:** 1. A non-human animal in which all of the somatic and germ cells contain DNA having SEQ ID NO: 1.
>
> 2. A non-human animal in which all of the somatic and germ cells contain DNA having SEQ ID NO: 2. [3. - 50. are identical in form to 1 and 2 with the sequence number corresponding with the claim number in each.]
>
> 51. A m thod of screening for potential causative agents which trigger or exacerbat Polycystic Kidney Diseas comprising administering a selected agent to a non-human animal of any one

of claims 1 -50 and observing the kidney of said animal for abundant cyst formation.

Analysis: The following analysis includes the questions that need to be asked according to the guidelines and the answers to those questions based on the above facts:

1) Based on the record, is there a "well established utility" for the claimed invention? **The specification as filed does not disclose or provide any evidence that points to a property of the claimed animals** (claims 1-50) such that another non-asserted specific and substantial credible utility would be well established. **Additionally, there is no art of record that discloses or provides any evidence that points to a property of the claimed animals** (claims 1-50) such that another non-asserted specific and substantial credible utility would be well established. With respect to claim 51, since it is directed to a specific method of use, the utility of this claim is limited to that use and the examiner should not look to a "well established utility" for the composition used in the claimed method. Consequently, the answer to the question is no.

2) **Has the applicant made any assertion of utility for the specifically claimed invention?**

Here, there is an asserted utility, i.e., to use the animals to research human genes from diseased human kidneys, specifically to use the animals in a method for screening for potential causative agents which trigger or exacerbate Polycystic Kidney Disease.

3) **Is the asserted utility specific?** The answer to this question is yes. In this case, the sequences (claims 1-50 and the full length counterparts of the other 7950 nucleic acid fragments) are asserted to be useful to generate the non-human animals as instantly claimed, and to use the animals in a screening method for PCK.

4) **Is the asserted utility substantial?** The answer to this question is yes because a disease model for PCK disease is a real world context of use.

5) **Is the asserted utility credible?** The answer to this question is no. **In this case it is noted in the specification that none of the 50 lines of mice that have been transformed with the claimed DNAs have developed Polycystic Kidney Disease to date. Additionally, there is no indication that the absence or pr s nc of a specific pr t in is associated with the disease c nditi n.** Thus, the conclusion that can be reached from this

analysis is that both a 35 U.S.C. § 101 rejection and a 35 U.S.C. § 112, first paragraph, rejection should be made.

Examiner's R j ction
Claims 1-51 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a credible asserted utility or a well established utility. Neither the specification as filed nor any art of record discloses or suggests any specific property or activity for the animals such that a utility would be well established for the animals.

Further, the claimed animals and method of screening are not supported by a credible utility because the specification states that none of the transgenic animals exhibited PCK disease. The asserted use of the animals is for research in human genes from diseased kidneys however the specification indicates that they were unable to get an operative model.

Since there is no evidence on the record that there are operative transgenic animal models for this research, the asserted utility is inoperative and is therefore not credible.

With regard to the asserted use of the animals as disease models, the action of the human DNA compounds on the animals is not specifically known and **the mere assertion that abundant cyst formation will be observable in any of the claimed animals** would not be accepted by one skilled in the art as being reasonable or credible in view of the contemporary knowledge in the art. As discussed by A. Cure et al. (a 1995 reference), while extensive studies have been conducted, the only clear results are from Mendelian studies of families that exhibit the disease. These studies indicate that the disease is inheritable and dominant, as opposed to recessive, via statistical analysis. No study has clearly indicated that a single DNA component is involved. No chromosomal loci have been identified. The possibility of a regulatory mechanism being involved has not been ruled out by any of the studies conducted to date. No specific protein or abnormal level of a specific protein has been associated with the disease.

The expectation that any of the claimed animals will exhibit the abundant cyst formation based on the presence of a single, unidentified DNA compound is not credible based on the specification's evidence to the contrary.

Claims 1-51 are also reject d under 35 U.S.C. § 112, first paragraph. Specifically, sinc the claimed invention is not

supported by either a credibl asserted utility or a well established utility for th reasons s t forth above, one skilled in the art would not know how to us the claimed invention so that it would operate as intended without undue experimentation.

Attorney Arguments Only (Alternative I)
Claims 1-51 have been rejected by the examiner under 35 U.S.C. § 101 and 35 U.S.C. § 112, ¶1. The examiner asserts that a substantial utility has not been disclosed. Reconsideration under 37 CFR 1.111 is requested.

The use of these animals to study DNA and polycystic kidney disease via observing abundant cyst formation is credible. This utility is directly analogous to that of US Patent No. 4,736,866 to Leder et al. In which human DNA compounds associated with tumor formation are contained in the genomes of non-human animals and these animals are used to study the human DNA compounds and tumor formation as well as tumor treatment. Such an important medical research utility as exists for the current claimed invention is a patentable utility. The claimed animals contain DNA compounds that are associated with human cells which exhibit the specific disease, just as they were in the Leder et al. patent.

Examiner's Response to Attorney Arguments Only (Alternative I)
Claims 1-51 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a credible asserted utility, or a well established utility for the reasons of record.

Claims 1-51 are rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility, or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the invention so that it would operate as intended without undue experimentation.

Applicants' arguments have been considered, but are not deemed persuasive. Applicants analogize the current specification, animals and intended utilities to those of Leder et al. US Patent No. 4,736,866. The situations are in fact not analogous. The specific embodiment of the specific MYC oncogene in the Leder et al. patent involved a well-established oncogene. There was no question in the art that the particular DNA compound had been directly associated with tumor formation in humans. Moreover, the specific mice disclosed in the Leder et al. specification exhibit tumor

formation. It does not directly follow that a diseased cell will necessarily contain "culprit" DNA as asserted by Applicants. This is particularly true of cDNA compounds as used herein, where no protein effect is associated with the diseas , nor are there any operative animal models that exhibit this disease state and the evidence of record is contrary to the desired result. Thus, even if one were to accept the premise that the diseased cell must contain a genetic flaw, no transgenic model is disclosed in currently available form.

Attorney Arguments with Evidence (Alternative II)

Claims 1-51 have been rejected by the examiner under 35 U.S.C. § 101 and 35 U.S.C. § 112, ¶1. The examiner asserts that a credible utility has not been disclosed. Reconsideration under 37 CFR 1.111 is requested.

In support of applicant's statement of utility, attached hereto is a declaration submitted under 37 CFR 1.132 by the inventors which describes a mouse corresponding to the animal of claim 38 which has exhibited abundant cyst formation. This effect has been confirmed as evidenced in the declaration, by the production of three additional founder mice that carry DNA SEQ ID NO: 38 as a transgene and have exhibited abundant cyst formation. In addition, as evidenced in the declaration, these mice have been cross-bred and some of their progeny exhibit the abundant cyst formation as well. Based on this evidence clearly the use of the claimed animals to screen for agents which trigger or exacerbate the disease condition is substantial and credible.

Examiner's Response to Attorney Arguments with Evidence (Alternative II)
The examiner should withdraw the rejection of claim 38 based on lack of credible utility in light of this evidence. However, the other product claims should still be rejected under 35 U.S.C. §101 and 35 U.S.C. §112 first paragraph as lacking credible utility and claim 51 should still be rejected under 35 U.S.C. §112 first paragraph as lacking an enabling disclosure except as it depends on claim 38. (Emphasis added.)

The applicant submits the pending claims define patentable subject matter. The above quoted Example 11 of the U.S. Patent Office Guidelines demonstrate as much and consideration of the following in this regard is requested.

In analyzing whether there is a credible utility for th claimed invention, the analysis of Example 11 concludes that there is not a "well established utility" for the claimed non-human animal in which all of the somatic and germ cells contain DNA having a fragment of a nucleotide sequence from a cDNA library made from kidney cells of a patient with Polysystic Kidney (PCK) Disease; or a method of screening for potential causative agents which trigger or exacerbate PCK disease which comprises administering a selected agent to the non-human animal and observing the kidney of the animal for abundant cyst formation. This conclusion of Example 11 is based, in part, on the finding that there is no art of record that discloses or provides any evidence that points to a property of the claimed animals such that another non-asserted specific and substantial credible utility would be well established.

In the present case however, the Examiner has asserted that Lia (Human Molecular Genetics 1998, Vol. 7, No. 8, 1285-1291) anticipates, i.e., teaches each and every aspect of, claims 1, 2, 5, 6, 20, 22, 23, 25-29, 46 and 55. See, Section 102 rejection spanning pages 18-19 of Paper No. 13. While not believing the Examiner to be correct in this regard, for the reasons further detailed below, the applicant notes that Lia teaches the following:

> "Recreating trinucleotide repeat instability in mice could thus provide a **useful** tool for studying mechanisms involved [in myotonic dystrophy]." See, page 1285, right column, first full paragraph of Lia. *[emphasis added]*

Accordingly, to the extent the Examiner believes the cited art anticipates the claimed invention, which it does not, the cited art provides evidence that points to a property of the claimed animals such that another non-asserted specific and substantial credible utility would be well established.

The claimed invention of Example 11 of the Guidelines was found to have satisfied the threshold inquiry of whether there was an asserted or well established utility in that the specification of the Example disclosed

> "to use the animals to research human genes from diseased human kidneys, specifically to use the animals in a method for screening for potential causative agents which trigger or exacerbate Polycystic Kidney Disease."

The present Examiner has recognized that the present specification asserts that the claimed mouse cells and sequences may be used (1) for determining whether expansion of a trinucleotide repeat in a TRP produces a phenotypic change; (2) for producing TRP gene products; and (3) for methods for the treatment of bone disease cartilage disease or kidney disease, by administering to an appropriate subject an agent capable of affecting the phenotype of a knock-out mouse. See, page 5-6 of Paper No. 13.

The specification further provides, for example at page 4, last two lines to page 6, that the present invention provides a mouse having a phenotype characterized by cartilage disease, such that cartilage formation is reduced. Moreover, mice of the present invention have bone disease, such as may be characterized by abnormal bone and reduced bone formation and/or chondrodysplasia. Finally, a mouse of the present invention may have a phenotype characterized by kidney disease, such as kidney malformation, including, optionally, renal dysplasia. The present specification further

indicates that the present invention is useful in providing a method of identifying agents capable of affecting one of the above-indicated phenotypes of the mice of the present invention. A further asserted (i.e., disclosed) utility of the present invention includes methods of treating bone disease, such as chondrodysplasia, and methods for ameliorating the symptoms of bone disease, such as shortened bones, abnormal growth plates and reduced vertebrae. Such methods include administration of T243 protein. Methods of treating cartilage disease and methods of ameliorating the symptoms of cartilage disease are also disclosed, for example. Accordingly, the applicant submits that the present specification contains assertions of utilities for the claimed invention.

Section 101 further requires, according to the Patent Office interpretation, that the asserted and/or well established utility be specific and substantial. Example 11 of the Guidelines found that the asserted utility was specific in that the recited sequences were asserted to be useful to generate the non-human animals of the claims and that the specification taught the use of the disclosed animals in a screening method for PCK.

In the present application, the specification teaches the use of the claimed nucleic acid sequences, proteins, cells, and animals to generate transgenic animals which demonstrate the above-noted specific phenotypes, to practice the above-noted specific methods. The proteins are further taught to be specific for the above-noted treatment methods. Further specific uses of the claimed invention are described and demonstrated throughout the specification. The disclosed "asserted" utility is specific.

The specification in Example 11 of the Guidelines was further found to have disclosed a substantial utility in that a disease model for PCK disease was a "real world context of use."

The applicant submits that the present disclosure of bone disease and/or kidney disease are "real world context of use" in a manner similar to that found to be sufficient in Example 11 of the Guidelines.

The disclosure of Example 11 of the Guidelines was ultimately found to have not taught a "credible utility" as the specification failed to provide evidence that any of the 50 lines of mice transformed with the claimed DNAs developed Polycystic Kidney Disease.

In the present application, the applicant has demonstrated that bone and kidney abnormalities develop with the claimed disruption of a target DNA sequence encoding a TRP, as claimed. Accordingly, the present application is submitted to teach at least one "credible utility".

The claims define patentable subject matter.

The Section 112, first paragraph, rejection of claims 1-47 and 53-56 stated on pages 7-16 of Paper No. 13 is moot in view of the above. The claims are supported by an enabling disclosure and the Examiner's consideration of the following in this regard is requested.

Initially, the applicant notes that the Examiner has separately alleged that the subject matter of claims 1-3, 12, 15, 16-18, 20, 22-30, 32-34, 45, 46 and 53-55 is already in the public domain, as allegedly evidenced by Hodgson (Hum. Mol. Genet. 1996, 5: 1875-1885). See, pages 16-18 of Paper No. 13 wherein these claims have

been rejected as allegedly b ing anticipated by Hodges. Moreover, the Examiner has alleged that the subject matter of claims 1, 2, 5, 6, 20, 22, 23, 25-29, 46 and 55 is allegedly already in the public domain, as evidenced by Lia (Hum. Mol. Gen. August 1998, 7: 1285-1291). See, pages 18-19 of Paper No. 13, wherein the indicated claims have been rejected as allegedly being anticipated by Lia. The Examiner's assertion that Hodges and Lia separately teach each and every aspect of the subject matter of claims 1-3, 5, 6, 12, 15, 16-18, 20, 22-30, 32-34, 45, 46 and 53-55 is inconsistent with the Examiner's separate assertion that one of ordinary skill in the art could not have made and used the invention of the indicated claims. The Examiner must either indicate that the claimed subject matter is patentable over the art of record or that the claims are enabled by the specification.

A review of the Examiner's further comments and the applicant's response is provided in the following wherein each of the Examiner's cited reference is discussed in the order presented by the Examiner.

Kappel ("Regulating gene expression in Transgenic Animals", Current Opinion in Biotechnology, 1992, 3: 548-553) is cited by the Examiner as evidence of the alleged unreasonable or undue amount of experimentation required as of 1999 (i.e., the filing date of the present priority application Serial No. 60/161,488) to make and use knock-out or transgenic animals. See, page 10 of Paper No. 13.

Kappel is a 1992 review article reporting on the state of the art between 1984 and 1992. Kappel, like all of the art cited by the Examiner, does not report on the methods of the applicants disclosure. Kappel is of little relevance therefore to whether

one of ordinary skill in the art could have used the applicant's disclosure to practice the claimed invention.

In any event, Kappel is noted to conclude that, even as of 1992,

> Transgenic animal technology is now well established as a critical method for analyzing gene expression and function. The approach continues to evolve, however, to include new strategies that offer a broad array of regulatory regimes. See, page 551, left column, "Conclusion", of Kappel.

Accordingly, contrary to the Examiner's assertion, Kappel confirms that one of ordinary skill in the art was routinely using "transgenic animal technology" to study targeted and regulated expression of genes and structural and functional ablation of genes.

The Examiner specifically relies on Kappel's teaching, at page 549, right column, second full paragraph, of

> cellular mechanisms [within the cells of transgenic animals] which prevent expression of the transgene, such as DNA methylation or deletion from the genome. See, page 10 of Paper No. 13.

Kappel refers in this regard to references 25 and 26 of Kappel. Reference 25 of Kappel (i.e., Engler et al "A Strain-specific modifier on Mouse chromosome 4 Controls Methylation of Independent Transgene Loci" Cell 1991, 65: 939-947), is summarized by Kappel (at page 552 of Kappel) as a report of a methylase mapped to mouse chromosome 4 wherein the authors apparently teach that passage of a transgene through SJL or DBA/2 mice results in under methylation whereas passage through C57BL/6 results in methylation- "suggest[ing] that the genetic background of mice may affect expression." (emphasis added). Accordingly, the Examiner has relied on a report by Kappel of Engler wherein "transg nic animal technology" has been optimized to

increase the efficiency of the creation of the desirabl result. Engler appears to have identified a problem and provid d a solution well before the applicant's use of the claimed invention.

Reference 26 of Kappel (i.e., Chaillet et al "Parental-specific methylation of an imprinted transgene is established during game to genesis and progressively changes during embryogenesis" Cell 1991, 66: 77-83) also apparently indirectly relied upon by the present Examiner, is reported by Kappel to identify stages of gametogenesis and embryogenesis where a gene is methylated and demethylated.

As noted previously, the applicant has demonstrated production of cells and transgenic animals within the claims. The optimization provided by the results reported in Kappel in 1992 led to the generally advanced level of skill in the art as of the time of the present invention. These reports do not support the Examiner's assertion that the present specification fails to teach one of ordinary skill in the art to make and use the presently claimed invention.

The Examiner has further relied on Mullins (Hypertension 1993; 22: 630-633) for the assertion that

> "not all animals express a transgene sufficiently to provide a model for disease as the integration of a transgene into difference [sic] species of animal has been reported to give divergent phenotypes." See, page 10 of Paper No. 13.

The applicant agrees with the conclusions of Mullins (1993) and again urges the Examiner to appreciate that the conclusions of Mullins (1993), like those of Kappel discussed above, form the background of advanced skill of the art of making and using transgenic animals and cells which were available to the applicants when the present invention was made. Mor importantly, the applicant notes that Mullins (1993) does not

state that the reported works of Hammer ("Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human β_2-m: an animal model of HLA-B27-associated disorders," Cell. 1990; 63: 1099-1112) with mice and rats required any undue amount of experimentation. Rather, Mullins (1993) reports that Hammer

> found that, whereas transgenic studies in the mouse failed to produce an adequate phenotype, the rat provided an informative disease model. See, page 6631, left column, lines 13-17 of Mullins.

Mullins (1993) in fact demonstrates that, even as of 1993, the art of transgenic manipulation was quite advanced. Specifically, Mullins (1993) reports that transgenic technology

> "has been extended to include a large number of species, such as the rat, rabbit, pig, sheep, goat, and cow." See, page 630, left column, third full paragraph of Mullins.

Mullins explains that the motivation as of 1993 to produce animals other than mice was the "size constraints in the mouse." Id. Mullins (1993) describes integration of the mouse *Ren*-2 renin gene **in rats** to produce a hypertension model (rat line TGRmRen 2-27); introduction of human apolipoprotein A-I gene **in a rat** to produce marked changes in lipid and apolipoprotein metabolism (see, page 631, left column of Mullins); studies on the secretion of alpha-lactalbumin into the milk of transgenic **rats** (id.); integration of a fusion gene consisting of mouse metallothionein promoter and the human growth hormone structural gene MT-hGH, **in rabbits**[1]; production of transgenic **sheep** using the MT-hGH construct (see, page 631, right column, last paragraph of Mullins);

[1] The applicant notes that the low integration frequency in rabbits as compared to mice was not considered to be unexpected or to diminish the utility or usefulness of making and/or using the transgenic rabbits. One of ordinary skill in the art will recognize that selection of successful transgenic integration is part of the process of making transgenic materials and that predictability and/or higher success rates are not required.

transgenic **sheep** expressing human factor IX; transgenic **sh ep** expressing human α_1-antitrypsin; transgenic **goats** expressing human tissue-type plasminogen activator in their milk; transgenic **pigs** expressing mouse whey acidic protein in the mammary gland; generation of transgenic **pigs** which express functional human hemoglobin (see, page 632 of Mullins); and transgenic **calves** carrying the human lactoferrin gene under bovine αS-casein regulatory elements (see, page 633 of Mullins). Mullins concludes that

> "Transgenesis is a tool for basic, clinical, and pharmaceutical research and with ongoing development will be refined [i.e., optimized] still further over the next decade. Id.

The Examiner's reliance of Mullins (1993) is appreciated as, quite to the contrary of the Examiner's assertions, Mullins (1993) demonstrates the generally advanced level of skill in the art as well as the appreciation that successful use of the "tool" of "transgenesis" does not require 100%, or even greater than 50%, "predictability".

The Examiner has relied on page 281 of Houdebine (Journal of Biotechnology 34 (1994) 269-287) for the assertion that

> "the elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene: e.g., specific promoters, presence or absence of introns, etc." See, page 10 of Paper No. 13.

While Houdebine states that construction of **efficient** vectors "turned out to be more complicated then anticipated," Houdebine does not teach that effective vectors, or even efficient vectors, required more than a reasonable amount of experimentation. Houdebine teaches that the problem of efficient vector construction was complex and that the process of testing new constructs to be expressed in cow milk is a "slow

process". Houdebine does not teach that methods of testing were unknown or that the construction of effective, or even efficient, vectors was impossible. In fact, it would appear that the slowest aspect of the testing related to the gestation period of cows as, according to Houdebine,

> "cell cultures are of little help... and transgenic animals must be obtained to test each vector. Only transgenic females can be directly used and the information concerning the vectors becomes available only when they are mature and lactate." See, page 281, left column of Houdebine.

Moreover, Houdebine states that while the construction of **efficient** vectors for expression of foreign genes in milk is not a problem solved in all cases,

> "there are some reasons to believe that, in future [sic], perhaps 80% of the transgenes will work in a satisfactory manner." Id.

While Houdebine may describe some areas of efficiently making and using transgenic technology which are slow, Houdebine does not indicate that the use of transgenic technology requires, as of 1993, an undue amount of experimentation. More importantly, the presently claimed invention does not require expression of transgenes in the milk of a cow, as was described to be complicated by Houdebine in 1993.

The Examiner relies on Wall (Theriogenology (1996) 45: 57-68) for an assertion that

> "'The position effect' and undefined control elements also are recognized to cause aberrant expression." See, page 10 of Paper No. 13

As noted above with regard to Mullins (1993), the ordinarily skilled artisan in the present art is able to make and use transgenic animals and cells even though 100% efficiency is not achieved. Th efficiencies described and optimizations desired in Wall and Mullins (1993) are, once perfected, likely to be the subject of future patent

applications. The fact that further development and optimization (i.e., "refining transgenic technology" according to Wall) may be useful or desirable does not diminish the fact that the present application, taken with the generally advanced level of skill in the art, teaches one or ordinary skill in the art to make and use the presently claimed invention.

Wall, like Mullins (1993), concludes

> "The tools for gene transfer are in hand, albeit the process is inefficient." See, page 64 of Wall.

Wall therefore recognizes that the tools transgenic technology are available and, like all tools, development and refinement are desirable. While many of the advances desired by Wall are now available, the present applicants should not be require to provide absolute predictability, as appears to be suggested by the Examiner, to teach one of ordinary skill to make and use the claimed invention.

Similar considerations are germane to the Examiner's reliance on Mullins (1996) ("Perspectives Series: Molecular Medicine in Genetically Engineered Animals: Transgenesis in the Rat and Larger Mammals", J. Clin. Invest., (April 1996) 97(7) 1557-1560). The Examiner quotes from Mullins (1996) summary that "a given construct may react very differently from one species to another." The relevance of this statement to the issue of enablement is not clear to the applicant.

Mullins (1996) reports that gene expression in vivo may be altered in many diverse ways. See, page 1557, first paragraph. Mullins notes that a problem with pronuclear microinjection is random integration of exogenous DNA. The positional effects noted by the Examiner to be described as a problem in Wall are described by Mullins (1996) as b ing

> "of greater concern in nonmurine transgen sis where the investment is higher." See, page 1558, left column.

Accordingly, the "positional effects" are, at most, an economic concern, as transgenic animals are apparently still produced. More importantly, Mullins (1996) indicates that the "positional effects", which concerned the Examiner in citing Wall, may apparently be overcome with position-independent, copy number-related expression using sequences such as the locus control regions identified upstream of the β-globin gene cluster and downstream of the CD2 gene, the A elements which flank the chicken lysozyme gene and matrix attachment regions. Id. More importantly, Mullins (1996) indicates that

> "such elements have been shown to function across species barriers, and their incorporation into gene constructs can overcome position effects and improve expression of heterologous genes within specific cell types. In many cases, simply including large amounts of flanking sequences may be sufficient to overcome position effects and direct expression". Id. (citations omitted).

Finally, Mullins (1996) indicates that use of techniques for cloning large segments of DNA, such as yeast artificial yeast artificial chromosome vectors (as utilized by Hodgson (1996), further described below) should greatly improve the chances of including important regulatory elements, including those involved in chromatin structure, within the transgene structure. Mullins (1996) therefore appears to teach that one of ordinary skill in the art had, as of 1996, tools to overcome any "positional effect" described as an impediment by Wall, and the Examiner, to making and using the presently claimed invention.

As for the Examiner's reliance on Mullins (1996) to state that different constructs react differently in separate species, the applicant notes that Mullins (1996) statement in this regard appears to be based on experiences using heterologous and homologous

promoters for organ-specific or tissue-specific targeting of expression. See, section of Mullins (1996) titled "Non Murine species in biomedical research". In such cases, the differences in "reactions" of constructs between species would appear to be expected and, in fact, a matter of specific design choice as opposed to a failing of the general utility of the tools of "transgenesis".

The Examiner relies on Cameron ("Recent Advances in Transgenic Technology", Molecular BioTechnology, Volume 7, 1997, pp 253-265) to allege that well regulated transgenic expression is not frequently achieved because of poor levels in the complete absence of expression or leaky expression in non-target tissue. See, page 11 of Paper No. 13. The presently claimed invention however does not require targeting to specific tissues such that the relevance of Cameron in this regard is not readily apparent. More importantly, Cameron is concerned, in the paragraph noted by the Examiner, with increasing the efficiency of a single construct in different transgenic lines. The applicants invention however does not require the use of a single construct but rather demonstrates methods of making a useful variety of constructs which should be applicable in a number of transgenic lines. Cameron describes the "position effects" as being

> "the result of the combined effects of chromatin configuration at the site of integration, compiled with the absence of "higher" *cis*-acting regulatory elements within the transgene construct." See, page 256 of Cameron.

Cameron goes on to report that Grosveld (Cell, 51, 97-985) reported high-level expression in every transgenic line produced when a ß-globin gene construct containing extensive flanking sequences was used. Id. Moreover, Grosveld apparently reported that the distinctive erythroid specific expression pattern that resulted was the result of

regulatory elements, termed a locus control region, buried within the flanking sequence. Accordingly, Cameron describes a previously recognized problem with efficiency as well as a solution reported by Grosveld, as similarly described by Mullins (1996). Cameron also indicates that a number of tissue-specific locus control regions (LCRs) were known at the time of the present invention. In addition to LCRs, Cameron also describes the existence and use of matrix attachment regions (MARs) or scaffold attachment regions (SARs) to confer position independence in stably transfected cell lines and transgenic mice.

The Examiner's reliance on the passages of ¶4 of Cameron which described previous difficulties experienced with transgenic expression, without also acknowledging the solutions to these difficulties reported by Cameron on pages 256-260 of the article, is not a complete and/or an accurate reflection of the level of skill in the art at the time of the present invention.

The Examiner relies on Sigmund (Arterioscler Thromb Vasc Biol 2000; 20: 1425-1429), which was published after the present priority date, to again express a concern regarding the random nature of transgene insertion and the possible effect of the same on transgene expression. The above comments are germane and the Examiner is again requested to appreciate that this concern relates to optimization of the efficiency of transgenic expression as opposed to difficulties in making and/or using the claimed invention.

The Examiner's reliance of Nieman ("Transgenic farm animals get off the ground" Transgenic Research 7, 73-75 (1998)) similarly demonstrates that transgenic pigs may be produced.

The Examiner concludes from all of the above-noted references that the claimed invention may not be made and/or used (see, sentence spanning pages 11-12 of Paper No. 13) however quite to the contrary, the references demonstrate that transgenic cells and animals, such as are the subject of the present claims, may be made and used without undue experimentation and the art has advanced to a stage where optimization of procedures have become the focus of further development. The applicants acknowledge, with appreciation, the Examiner recognition that the specification is enabling for the exemplified transgenic mouse whose genome comprises a knock-out in the T243 gene. The applicants submit however that, given the advanced level of skill in the art, one of ordinary skill would be able to make and use the claimed invention.

The Examiner's reliance on Moreadith (Journal of Molecular Medicine (1997) 75: 208-216) is noted (see, page 12 of Paper No. 13) however the applicant believes that the presently claimed invention has been demonstrated to be enabled, for the reasons noted above and recitations of specific phenotypes in the claims should not be required. The applicants have demonstrated that a reduction in TRP produces the described phenotype.

The claims are submitted to be supported by an enabling disclosure.

The Section 112, second paragraph, rejection of claims 2-4, 10-18, 25, 29-47, 54, 56 and 57 stated on page 16 of Paper No. 13 is moot. The claims have been amended with the Examiner's comments and objections in mind and the claims are submitted to be definite.

The Section 102 rejection of claims 1-3, 12, 15, 16-18, 20, 22-30, 32-34, 45, 46 and 53-55 over Hodgson (Human Molecular Genetics, 1996, 5: 1875-1885) is moot.

The claims are submitted to be patentable over the cited art. As not d above, the claims have been amended to advance prosecution and ar believed to be consistent with subject matter indicated by the Examiner to be patentable over Hodgson. Of the new claims, only claims 77-79 and 81-84 (corresponding, in part, to now canceled claims 22-24 and 32-33) were not previously specifically indicated as being allowable over the cited art. The applicants note however that as Hodgson indicates in the Abstract, for example, that homozygous targeted disruption of the murine HD gene results in embryonic lethality, and that FVB/N mice expressing the YAC transgene were mated to mice heterozygous for the murine HD gene disruption (see, page 1884, left column, last paragraph of the reference), the recitation of homozygous disruption in these indicated claims is believed to define over the art. Moreover, claims 81-83 describe the target DNA sequence in a manner considered in now-canceled claim 19 (corresponding to new claim 75) to be patentable over the cited art. Moreover, Hodgson is concerned with restoring expression of human huntingtin in mice with a yeast artificial chromosome. The presently claimed invention however requires a disruption in a target DNA sequence encoding a TRP which, according to specification, requires a reduction in the production of wild-type TRP. See, page 5, lines 12-15 of the specification. Hodgson on the other hand provides a restoration of protein production. As Hodgson fails to teach each and every aspect of the presently claimed invention, the claims are submitted to be patentable over the same.

The Section 102 rejection of claims 1, 2, 5, 6, 20, 22, 23, 25-29, 46 and 55 over Lia (Human Molecular Genetics, August 1998, 7: 1285-1291), is moot.

The pending claims are submitted to be patentable over the cited art. As noted above, the claims have been amended to advance prosecution and ar believed to be consistent with subject matter indicated by the Examiner to be patentable over Lia. Of the new claims, only claims 77 and 78 (corresponding, in part, to now canceled claims 22 and 23) were not previously specifically indicated as being allowable over the cited art. As Lia is not believed to teach homozygous disruptions, as claimed, the claims are submitted to define over the art. Moreover, Lia does not require a reduction of production of wild-type protein, as required by the presently claimed invention. That is, Lia teaches that the affected trinucleotide repeat is contained in the 3'-untranslated region of the DM protein kinase gene (DMPK) on chromosome 19. See, page 1285, right column of Lia. There is no indication in Lia that production of the wild-type kinase had been inhibited. Moreover, Lia indicates that there was no correlation found between a level of somatic CTG repeat instability and a level of transcripts of the human gene in transgenic mice, suggesting that production of the wild-type protein is not inhibited. See, page 1289, right column of Lia. As Lia fails to teach each and every aspect of the presently claimed invention, the claims are submitted to be patentable over Lia.

In view of the above, the claims are submitted to be in condition for allowance and a Notice of that effect is requested.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Delete the paragraph spanning lines 8-15 of page 1 and insert the following therefor:

Many polymorphic trinucleotide repeats have been identified in the human genome. These mutations are produced by heritable, unstable DNA and are termed "dynamic mutations" because of changes in the number of repeat units inherited from generation to generation (Koshy, *et al.*, *Brain Pathol,* 7:927-42 (1997)). Although these repeats are highly polymorphic, their number usually does not exceed 40 repeats in normal individuals (Online Mendelian Inheritance in Man, OMIM (TM). Johns Hopkins University, Baltimore, MD. MIM Number: 603279: jlewis :7/14/1999; World Wide Web URL: [http://www.]ncbi.nlm.nih.gov/omim; Koshy, *et al.* (1997)).

Delete the paragraph spanning lines 1-20 of page 11, and insert the following therefor:

The term "homologous recombination" refers to the exchange of DNA fragments between two DNA molecules or chromatids at the site of homologous nucleotide sequences, i.e., those sequences preferably having at least about 70 percent sequence identity, typically at least about 85 percent identity, and preferably at least about 90 percent identity, alternatively, at least about 95-98 percent identity. Homology and/or percent identity can be determined using a "BLASTN" algorithm, such as BLAST (Basic Local Alignment Search Tool) 2.0, available on-line at [http://www.]ncbi.nlm.nih.gov:80/BLAST/, (Basic, Advanced or PSI) and as described in

any of Altschul, S.F., Gish, W., Miller, W., My rs, E.W. & Lipman, D.J. (1990) "Basic local alignment search tool." J. Mol. Biol. 215:403-410. (Medline); Gish, W. & States, D.J. (1993) "Identification of protein coding regions by database similarity search." Nature Genet.3:266-272. (Medline); Madden, T.L., Tatusov, R.L. & Zhang, J. (1996) "Applications of network BLAST server" Meth. Enzymol. 266:131-141. (Medline); Altschul, S.F., Madden, T.L., Schäffer, A.A., Zhang, J., Zhang, Z., Miller, W. & Lipman, D.J. (1997) "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs." Nucleic Acids Res. 25:3389-3402. (Medline); and Zhang, J. & Madden, T.L. (1997) "PowerBLAST: A new network BLAST application for interactive or automated sequence analysis and annotation." Genome Res. 7:649-656. (Medline) It is understood that homologous sequences can accommodate insertions, deletions and substitutions in the nucleotide sequence. Thus, linear sequences of nucleotides can be essentially identical even if some of the nucleotide residues do not precisely correspond or align.